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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/776,252	02/02/2001	Andrew Ellington	D 6296	9740

7590 11/26/2002

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EXAMINER	
ZITOMER, STEPHANIE W	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 11/26/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/776,252	ELLINGTON et al.
Examiner	**Art Unit**
S. Zitomer	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Aug 29, 2002*.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 2, 5-12, 15, 17-25, and 28* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 2, 5-12, 15, 17-25, and 28* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☒ The proposed drawing correction filed on *Aug 29, 2002* is: a) ☒ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Application status

1. Receipt of the Response and Amendment under 37 CFR 1.111 filed August 29, 2002 is acknowledged.

2. Informalities, objection to the specification and rejections under 35 U.S.C. 112, second paragraph, set forth in the previous Office action, paper no. 6 mailed March 29, 2002, have been withdrawn in view of corrections to the specification and amendments to the claims. Applicant's comments thereto have been fully considered. The rejection of claims 1-3, 15-17, 19, 23, 25, 26 and 28 under 35 UDC 102(b) over Royer (5,445,935) has been withdrawn as superfluous in view of the other two 102 rejections. Applicant's arguments thereto, combined the arguments to the other 102 rejections, have been fully considered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Rejection under 35 U.S.C. 112, second paragraph: Indefiniteness

3. Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The recitation "further comprises an electrochemical signal or an enzyme signal" lacks antecedent basis in claim 1 because it conflicts with the claim recitation "wherein the signal is an optical signal expressed as fluorescence intensity or colorimetric intensity".

Rejections under 102(b): Anticipation

4. Claims 1, 2, 5-12, 15, 17, 19, 23 and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by the patent to Pitner et al. (5,650,275). Regarding claim 1, Pitner et al. disclose the claimed invention method of detecting a differential signal of a signaling aptamer (detectably labeled nucleic acid ligand) upon binding a ligand (target compound), the differential signal generated by a reporter molecule (spectroscopically detectable label) comprising the steps of contacting (mixing) the signaling aptamer (spectroscopically detectably labeled nucleic acid ligand) with the ligand (target compound) wherein the former binds (complexes with) the latter and detecting the differential signal generated by the

reporter molecule (spectroscopically detectable label measured before and after binding) at columns 13-14, claim 1, wherein the differential signal is an optical signal expressed as fluorescence intensity (column 5, lines 22-24). The instant claim recitation "transducing the conformational change of a signaling aptamer that occurs upon the signaling aptamer binding a ligand to a detectable differential signal" is inherent in the claim 1 method of Pitner et al. because it was known in the prior art as set forth in the "Description of the Related Art" section of the instant specification that aptamers (nucleic acid ligands) "undergo an 'induced fit' conformational change in the presence of their cognate ligands, and thus an appended dye easily undergoes a ligand-dependent change in its local environment". *In re Spada*, 911F.2d 705, 15 USPQ2d 1650 (Fed. Cir. 1990). (Inherency of property or method steps in reference. MPEP 2112.01) Also see Pitner et al. at column 2, lines 55-59).

Regarding claims 2 and 7-9, Pitner et al. disclose the claimed method embodiment wherein the differential signal comprises an optical signal which is fluorescence, polarization or lifetime wherein the reporter molecule is a fluorescent dye and the latter is fluorescein (column 3, line 64-column 4, line 7; column 4, lines 56-59).

Regarding claims 5 and 6, Pitner et al. disclose the claimed method embodiment wherein the signaling aptamer comprises a reporter molecule appended to an aptamer (nucleic acid ligand) by covalent coupling (column 4, lines 21-27) during chemical synthesis (column 4, lines 28-43).

Regarding claims 10-13, Pitner et al. disclose the claimed method embodiment wherein the aptamer (nucleic acid ligand) is DNA (column 8, Example 2); the ligand (target compound) is not a nucleic acid (column 3, lines 23-48); the ligand (target compound) is in solution and the signaling aptamer (labeled nucleic acid ligand) is in solution (columns 9-10, Example 3).

Regarding claim 15, Pitner et al. disclose the claimed invention method of detecting an optical signal of a signaling aptamer (detectably labeled nucleic acid ligand) upon binding a ligand (target compound), the optical signal generated by a fluorescent dye comprising the steps of contacting (mixing) the signaling aptamer (fluorescently labeled nucleic acid ligand) with the ligand (target compound) wherein the former binds (complexes with) the latter and

detecting the optical signal generated by the fluorescent dye (measured before and after binding)) at columns 13-14, claim 1 and column 3, line 64- column 4, line 7. The instant claim recitation "transducing the conformational change of a signaling aptamer that occurs upon the signaling aptamer binding a ligand to a detectable optical signal generated by a fluorescent dye that is appended to the signaling aptamer at a site that not does not interfere with a ligand-binding site of the signaling aptamer prior to binding the ligand" is inherent in the claim 1 method of Pitner et al. because it was known in the prior art as set forth in the "Description of the Related Art" section of the instant specification that aptamers (nucleic acid ligands) "undergo an 'induced fit' conformational change in the presence of their cognate ligands, and thus an appended dye easily undergoes a ligand-dependent change in its local environment" and because Pitner et al. shows in the results obtained in Example 5 (columns 11-12) that the internally appended fluorescent dye does not interfere with the binding site of the aptamer (nucleic acid ligand). *In re Spada*, 911F.2d 705, 15 USPQ2d 1650 (Fed. Cir. 1990). (Inherency of property or method steps in reference. MPEP 2112.01) Also see Pitner et al. at column 2, lines 55-59).

Regarding claims 17 and 19 Pitner et al. disclose the claimed method embodiments of claim 15 wherein the fluorescent dye is appended to a nucleic acid binding species (aptamer) (nucleic acid ligand) by covalent coupling (column 4, lines 21-27); and the fluorescent dye is fluorescein (column 3, line 64-column 4, line 1).

Regarding claim 23, Pitner et al. disclose the claimed method embodiment wherein the ligand (target compound) is a molecule bound by the signaling aptamer wherein the molecule is not a nucleic acid (column 3, lines 23-48)

Regarding claim 25, Pitner et al. disclose the claimed method embodiment wherein the ligand (target compound) is in solution (columns 9-10, Example 3).

Rejections under 102(e): Anticipation

5. Claims 1, 2 and 7-12 are rejected under 35 U.S.C. 102(e) as being anticipated by the patent to Gold et al. (6,242,246). Regarding claim 1 Gold et al. disclose the claimed invention method of detecting a differential signal of a signaling aptamer (detectably labeled nucleic acid ligand) upon binding a ligand (target molecule), the differential signal generated by a reporter molecule (fluorescent label) comprising the steps of contacting the signaling

aptamer (fluorescent labeled nucleic acid ligand) with the ligand (target molecule) wherein the former binds the latter and detecting the differential signal generated by the reporter molecule (measured before and after binding)) in the Abstract, lines 2-14, column 15, lines 49-53 and column 16, lines 54-57. The instant claim recitation "transducing the conformational change of a signaling aptamer that occurs upon the signaling aptamer binding a ligand to a detectable differential signal generated by a reporter molecule that is appended to the signaling aptamer [nucleic acid ligand] prior to binding the ligand [target molecule]" is inherent in the claim 1 method of Gold et al. because Gold et al. disclose that the "labels on such ligands [aptamers] undergo a detectable change in fluorescence intensity, fluorescence polarization or fluorescence lifetime upon binding of the nucleic aid ligand [aptamer] to its target molecule [ligand]" (column 15, lines 49-52). Furthermore, it was known in the prior art as set forth in the "Description of the Related Art" section of the instant specification that aptamers (nucleic acid ligands) "undergo an 'induced fit' conformational change in the presence of their cognate ligands, and thus an appended dye easily undergoes a ligand-dependent change in its local environment". *In re Spada*, 911F.2d 705, 15 USPQ2d 1650 (Fed. Cir. 1990). (Inherency of property or method steps in reference. MPEP 2112.01) Also see Gold et al. at column 15, lines 49-52 and column 16, lines 54-56 and Pitner et al. at column 2, lines 55-59).

Regarding claim 2, Gold et al. disclose the claimed method embodiment wherein the differential signal comprises an electrochemical signal (columns 17-18 at V.A.)

Regarding claims 7-9, Gold et al. disclose the claimed method embodiment wherein the reporter molecule is appended to aptamer (nucleic aid ligand) by covalent coupling (column 15, lines 46-49), the reporter molecule is a fluorescent dye and the latter is fluorescein (column 15, lines 49-53).

Regarding claims 10-12, Gold et al. disclose the claimed method embodiment wherein the aptamer (nucleic acid ligand) is RNA, DNA, modified RNA or modified DNA (column 5, paragraph at 4.); the ligand (target molecule) is a molecule bound by the signaling aptamer (nucleic acid ligand) (column 15, lines 44-61) and the molecule is not a nucleic acid (column 6, lines 2-4); the ligand (target molecule) is in solution and the signaling aptamer (labeled nucleic acid ligand) is in solution (column 9, lines 10-13).

Rejections under 35 U.S.C. 103(a): Obviousness

6. Claims 18, 20-22 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pitner et al. (5,650,275) as applied to claims 1, 2, 5-12, 15, 17, 19, 23 and 25 above (paragraph 4), and further in view of Gold et al. (6,242,246), Conrad (5,728,525) and Szostak et al. (5,631,146). Regarding claim 18, the claimed method embodiment differs from the method of Pitner et al. wherein the fluorescent dye replaces a nucleic acid residue in the aptamer or is inserted between two nucleic acid residues in the aptamer wherein the placement does not interfere with the ligand-binding site of the aptamer. However, it was known in the art as taught by Conrad to substitute a fluorescent dye for a nucleic acid residue in a polynucleotide during chemical or enzymatic synthesis (column 12, lines 46-63). It would have been obvious and the skilled practitioner in the art would have been motivated at the time the claimed invention was made to label the nucleic acid ligand of Pitner et al. by replacing a nucleic acid residue with a fluorescent dye by the obvious benefit of ease and economy of labor in replacing the residue during chemical or enzymatic synthesis.

Regarding claims 20-22 and 24, the claimed method embodiment differs from the method of Pitner et al. wherein the aptamer (nucleic acid ligand) is an anti-adenosine RNA or DNA aptamer wherein the former is ATP-R-Ac13 and the latter is DFL7-8 and the ligand (target molecules) is adenosine. However, Pitner et al. note that numerous nucleic acid ligands that bind target molecules have been identified and cite a paper by Sassanfar and Szostak disclosing anti-adenosine triphosphate nucleic acid ligands (RNA aptamers) and the Szostak et al. patent teaches anti-adenosine triphosphate and anti-adenosine DNA aptamers prepared by the same process (column 4, line 56-column 5, line 9). It would have been obvious and the skilled practitioner in the art would have been motivated at the time the claimed invention was made to employ an anti-adenosine aptamer in the method of Pitner et al. in view of the Pitner et al. teaching such aptamers (nucleic acid ligands) were known in the art and in view of the known benefit of employing an aptamer that was known and proven in the art and readily obtainable by synthesis of the published nucleotide sequence. It would have been obvious further to synthesize aptamer analogues of the claims 21 and 22 aptamers in view of the teaching of Szostak et al. of a large number of anti-adenosine

aptamers having the same conserved region as the aptamer of claim 22 (Figure 4A) and the methods for producing them wherein such aptamers would have been expected by one of ordinary skill in the art to function in the same manner as the aptamers of claims 21 and 22 in view of the reference teaching that the conserved regions are the critical adenosine binding regions (column 7, lines 29-35 and column 8, lines 47-52).

7. Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pitner et al. (5,650,275) as applied to claims 1, 2, 5-12, 15, 17, 19, 23 and 25 above (paragraph 4), and further in view of Royer (5,445,935). The claimed method embodiment of claim 28 differs from the method of Pitner et al. wherein the ligand (target molecule) of claim 15 is quantitated by a method wherein the signaling aptamer (fluorescent labeled nucleic acid ligand) binds the ligand and the increase in the optical signal generated by the fluorescent dye resulting from the binding is correlated with the quantity of ligand bound to the signaling aptamer. However, Royer teaches a method for quantitating a ligand (macromolecule) wherein a fluorescent labeled polynucleotide (signaling aptamer) binds the macromolecule (ligand) and the increase in the optical signal generated by the fluorescent dye resulting from the binding wherein the optical signal positively correlates with the quantity of ligand bound to the signaling aptamer at column 17, claim 1, column 19, lines 8-10, Abstract, lines 9-12. It would have been obvious and the skilled practitioner in the art would have been motivated at the time the claimed invention was made to combine the quantitative method of Royer with the method of Pitner et al. in view of the teaching of Pitner et al. that their method can be used to quantitatively determine the presence of a target molecule (ligand) (column 3, lines 1-2 and column 4, lines 63-66) and further in view of the similarity of the Royer and Pitner et al. methods with regard to the binding (complexing) of a macromolecule (target molecule) with a fluorescently labeled polynucleotide (nucleic acid ligand) and the measuring of fluorescence polarization.

Response to applicant's arguments

8. Applicant's arguments filed August 29, 2002 have been fully considered but they are not persuasive. Regarding the argument against the 102(b) rejection over Pitner et al. that the polarization measurements of Pitner et al. depend on "solvent diffusion and tumbling motion of the fluorescent molecule" and the slowing of the tumbling on binding of a

"fluorescently labeled receptor molecule [binds] with the target compound" due to a size increase of the target compound, it is noted that these effects, solvent diffusion, tumbling motion and slowing of tumbling on binding, are also occurring in the claimed invention method because the latter is the same as that of Pitner et al. with regard to method steps. Furthermore, any energy transduction from the conformational change to the fluorescent label in the claimed invention method necessarily also occurs in the reference method because the nucleic acid ligand (aptamer) free in solution binds the target (ligand) in the same way as in the claimed invention method. The arguments next attempt to draw a difference between the claimed invention method and that of the reference based on measuring techniques which, however, do not distinguish the claimed invention method over the prior art absent some unexpected result. In fact, the same effect of conformational change due to binding, the intensity of the fluorescence emitted by the reporter molecule, is measured in both instances. See Pitner et al. at column 5, lines 22-24 and column 6, lines 6-8. Additionally, the broad claim language encompasses the reference step of measuring the intensity of the fluorescence after subjecting it to polarization. The further argument that Pitner et al. "requires a two-step comparative measurement" appears to imply that this is somehow in contrast to the claimed invention method. On the contrary, applicant's method also requires comparative measurements as clearly recited in the claim word "differential". The argument that the "position [of the fluorophore] within the aptamer determines whether or not it fluoresces" on binding and conformational change is impermissibly directed to a limitation not recited in the claims nor is the statement that "an appended dye in the instant invention does not necessarily undergo a ligand-dependent change in it s local environment sufficient enough to induce simple fluorescence". See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The latter statement seems to suggest that the claimed invention method is not reliable or depends for operability on other, unrecited, parameters.

Regarding the 102(e) rejection over Gold et al. the implied argument that the amendments to claims 1 and 15 "to recite the signaling aptamer as being in solution" distinguish over Gold et al. in which the labeled nucleic acid ligands are attached to a biochip fails because Gold et al. specifically point out that the nucleic acid ligands are

attached to crosslinking agents such as ethylene glycol oligomers "so that the subsequent attachment of the Nucleic acid ligands and their interaction with Target molecules **will occur in solution**" (emphasis added) (column 9, lines 9-14). Furthermore, it is pointed out that the broad claim language encompasses the reference method step of attaching the nucleic acid ligands (aptamers) to a biochip. **Notably**, the arguments then state that Gold et al. disclose that "binding of the target can be determined by measuring a change in fluorescence intensity, fluorescence polarization, fluorescence anisotropy and fluorescence lifetime (col. 15, lines 42-65)" which supports the point made earlier in rebuttal that the manner of measuring the fluorescence is not a patentable distinction: it is a matter of choice. Regarding the 103(a) rejection over Pitner et al. in view of Conrad and Szostak et al. the argument that the suggested combination wherein "aptamers bind an appropriate ligand, and containing a fluorescent dye...do not fluoresce upon contact with the ligand (pg. 15, line 27-pg. 16, line 23)" cannot be supported by the cited passage because it cannot be found in any of the references or the specification. The further argument that "Pitner et al. itself does not teach not suggest Applicant's method as recited in amended claims 1 and 15" has been rebutted at the beginning of this section. As to the combination of Royer and Pitner et al. in the rejection of claim 28 the argument that the references do not teach measurement of fluorescence intensity was also previously rebutted.

Conclusion

9. No claim is allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action.

In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephanie Zitomer whose telephone number is (703) 308-3985. The examiner can normally be reached on Monday through Friday from 9:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152. The official fax phone number for this Group is (703) 308-4242. The unofficial fax number is (703) 308-8724. The examiner's Rightfax number is 703-746-3148.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196..

S. Zitomer

Stephanie Zitomer, Ph.D.

November 22, 2002

STEPHANIE W. ZITOMER
PRIMARY EXAMINER